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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,132	11/15/2001	Brian A. Fox	00-62	5882

7590 07/01/2003

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EXAMINER
KAPUST, RACHEL B

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,132	FOX ET AL.	
	Examiner	Art Unit	
	Rachel B Kapust	1647	

-- Th MAILING DATE of this communication app ars on th cov r sh t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *9-17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claims 1-8 and 18 (Group I) as drawn to SEQ ID NO: 2 and the species election of an immunoglobulin constant region in Paper No. 8 is acknowledged. Claims 1-19 are pending in this application. Claims 9-17 and 19 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-8 and 18 are under examination as they pertain to SEQ ID NO: 2.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The disclosure is objected to because of the following informalities:

The specification does not contain a separate section pointing out the Brief Description of the Drawings in accordance with 37 CFR § 1.74. While figures 1-3 are described on pages 5 and 6 of the specification, the specification is missing a section heading. Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 4 is objected to because upon cancellation of non-elected matter, claim 4 will become a substantial duplicate of claim 1. Accordingly, it is suggested that claim 1 be amended and claim 4 canceled.

Claims 5 and 18 are objected to because of the following informalities:

Claim 5 is objected to for containing grammatical errors within the Markush group. There is a period following the second defined region within the group. It is the Examiner's understanding that this is intended to be a semi-colon instead of a period. In addition, only one "and" is necessary prior to the last defined region. Appropriate correction is required.

Claim 18 is objected to for depending from a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 and 18 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 1-8 and 18 are drawn to isolated polypeptides comprising defined regions of SEQ ID NO: 2. The specification discloses a new human polypeptide designated "zcub5." Applicants assert that the amino acid sequence of zcub5 shows significant homology to neuropilin-1.

The claimed polypeptide is not supported by either a specific and substantial asserted utility or a well-established utility.

A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" use for the claimed invention. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966):

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

The specification fails to provide objective evidence of any activity of this protein. Cell-specific expression and drug delivery, as taught on page 36, would not be specific to the claimed polypeptide, nor does the specification teach any particular specificity. Similarly, the use of

zcub5 as a standard (p. 44) is not specific to the protein. Further, while applicant lists a number of diseases in which the protein might be involved (p. 34 line 30 through page 35, line 17), the specification does not disclose any diseases or conditions known to be associated with the encoded protein. Thus, further research is required to identify a disease for which it could be used, or a disease for which its presence would be diagnostic. Therefore, there is no substantial utility associated with the identification of modulators of zcub5 (p. 37). There is no "real world" use for modulators of a protein whose function is unknown. See Brenner v. Manson, noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

The invention also lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. Applicants assert that the claimed zcub5 proteins have putative CUB, factor V/VIII, transmembrane, and intracellular domains and that the proteins have significant homology to neuropilin-1. As such, applicants assert that "the zcub5 proteins are characterized by...their ability to bind to members of the PDGF/VEGF family of growth factors and/or to semaphorins" (page 28, lines 35-36). However, there is no well-established utility associated with identification of zcub5 as related to neuropilins. For instance, while it is known that neuropilin-1 plays a role in regulating developmental angiogenesis, the activity of neuropilin-1 and the mechanisms by which neuropilin-1 regulates angiogenesis still need to be elucidated (see Lee *et al.* (2002), *Proc. Natl. Acad. Sci.* 99: 10470-10475). Similarly, Takahashi *et al.* (1998) teach that neuropilins are sufficient to determine semaphorin

responsiveness and that SemA and SemE are SemD-blocking antagonists of neuropilin-1, however the utility associated with neuropilins is not well established.

Moreover, nothing is known about the developmental effects of neuropilin-2, a member of the neuropilin family (Gluzman-Poltorak *et al.* (2000) at p. 18044, column 1). One of ordinary skill in the art would not know what developmental effects are in common between members of the neuropilin family. Gluzman-Poltorak *et al.* also teach that there is no clear-cut evidence indicating that the binding of VEGF family members to neuropilin-1 or neuropilin-2 results in signal transduction in endothelial cells or in any other cell type (p. 18044, column 1). Thus, further research would be required before one of ordinary skill in the art would know how to use neuropilins and anything related to them.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Moreover, the specification does not reasonably provide enablement for biologically active variants of SEQ ID NO: 2 comprising the various regions disclosed in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of patent protection sought by Applicants as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al.* (1990), *Science* 247: 1306-1310, especially p. 1306, column 2, paragraph 2; Wells (1990), *Biochemistry* 29: 8509-8517; Ngo *et al.* (1994), The Protein Folding Problem and Tertiary Structure Prediction, Merz *et al.*, eds., Birkhauser, Boston, pp. 14-16).

However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue

experimentation, the positions in the protein that are tolerant to change and the nature and extent of changes that can be made in these positions. In particular, SEQ ID NO: 2 is a polypeptide consisting of 715 amino acids. The claims are drawn to polypeptides comprising regions of SEQ ID NO: 2 from about 100 amino acids in length to about 400 amino acids in length. These polypeptides could have structures that are very different from that of SEQ ID NO: 2. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-8 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides comprising only a portion of the disclosed sequence. Such polypeptides vary substantially in length and composition, and could have very different structural and functional characteristics from the polypeptide of SEQ ID NO: 2, since they are only required to have approximately 100 amino acids in common. Applicant has not described any common characteristics linking these different polypeptides so that the skilled artisan could identify which ones would be members of a genus of polypeptides having similar properties. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Since they required common region is only a small part of the sequence, it is not sufficient to impart any characteristic physical, structural or functional features to the invention. The skilled artisan thus cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the method of isolation, nor can the artisan distinguish zcub5-like molecules from other neuropilin-related molecules. The claims further do not require any particular function that would serve to identify the molecules encompassed by the genus so that

one of skill would recognize that Applicants were in possession of them, nor have Applicants disclosed any such function in the specification. Thus, the specification does not describe the characteristics of the genus of zcub5-like polypeptides in such a way as to convey to one of skill in the art that the inventor was in possession of this genus as broadly claimed.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mondays-Fridays 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 892-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK
June 30, 2003